

## **REMARKS**

### **I. Status of the Claims**

Claims 1-3, and 8-10 are currently under examination on their merits.

### **II. Withdrawal of Previous Claim Rejections Under 35 U.S.C. §112 Second Paragraph**

Applicants acknowledge the Action's withdrawal of claim rejections under 35 U.C.S. § 112, second paragraph.

### **III. Claim Rejections Under 35 U.S.C. §102(b)**

Claims 1-3, and 8 stand rejected under 35 U.S.C. §102(b) in view of U.S. Patent No. 5,723,313 by Sherr et al. (hereinafter "Sherr et al."). Specifically, the Action asserts that the transitional phrase "has" is considered as open as to the scope of the claimed protein. The Action further asserts that the phrase "p19ARF protein fragment that has the amino acid sequence as set forth in SEQ ID NO:10" is interpreted to include the full-length protein allegedly taught by Sherr et al. Applicants respectfully traverse.

The Action's position that the phrase "p19ARF protein fragment that has the amino acid sequence as set forth in SEQ ID NO:10" would encompass the full-length p19ARF protein is misplaced. During examination, the entire claim must be considered and words constituting express limitations cannot be ignored. MPEP §2163.II.A.1. Here, Applicants respectfully contend that the Office ignores the claim term "fragment" and assert that the claim directed to a p19ARF fragment has the same scope as the full-length protein.

Applicants respectfully submit that "protein fragment" refers to a peptide that is less than the full length protein. During examination, the Office must give words of the claim their plain meaning unless applicant has provided a clear definition in the specification. MPEP §2111.01 I. The plain meaning refers to the ordinary and customary meaning given to the term by those of ordinary skill in the art. MPEP §2111.01 II.

Examples of using the term protein or peptide "fragments" as meaning less than the full-length protein are legion. These include, for example, the Klenow fragment of DNA polymerase I from *E. coli* (<http://www.vivo.colostate.edu/hbooks/genetics/biotech/enzymes/klenow.html>);

Diphtheria toxin A fragment (<http://textbookofbacteriology.net/diphtheria.html>); cystatin in multiple sclerosis ([http://www.hopkinsmedicine.org/Press\\_releases/2006/03\\_03\\_06.html](http://www.hopkinsmedicine.org/Press_releases/2006/03_03_06.html)); and antibody fragments such as F(ab), F(ab)' and F(ab)<sub>2</sub> ([www.nature.com/nbt/journal/v23/n9/abs/nbt1142.html](http://www.nature.com/nbt/journal/v23/n9/abs/nbt1142.html)). Applicants submit that the art-recognized meaning of the term protein or peptide “fragment” is less than the full-length version of the corresponding protein. The ordinary and customary meaning of the term “protein fragment” to one having ordinary skill in the art would thus refer to an incomplete part of the full-length protein. One of ordinary skill in the art would understand the scope of the claim to be a peptide that is short of the full-length protein.

Moreover, the specification does not provide, nor does the Action assert otherwise, an explicit definition of “fragment” that contradicts the ordinary and customary meaning of the term. Additionally, the term “fragment” is used in the specification in a way consistent with its ordinary and customary meaning. For example, on page 36, the last paragraph of the specification describes that a “fragment” of DNA can be obtained by restriction digest of a “larger” piece of DNA. (Emphasis added) On page 48, the second paragraph of the specification discloses that DNA encoding a dominant negative mutant polypeptide of FoxM1B or FoxM1B activity inhibiting “peptide fragment thereof” can be prepared and introduced into the cells. (Emphasis added). Similar examples can be found, for example, on pages 38, 45, and 71 of the specification. Thus, throughout the application, the term “fragment” is consistently used to refer to a portion smaller than the whole. The Action’s assertion that a p19ARF protein fragment would encompass the full-length protein is improper, because the assertion contradicts the ordinary meaning of the term and is inconsistent with the specification.

In addition, Applicants remind the Office that the pending claims are method claims. The cited reference does not teach that contacting a tumor cell with the full-length protein would be capable of inhibiting proliferation of the tumor cell; rather, the reference teaches that the full-length protein must be expressed in the tumor cell. Applicants respectfully contend that in order to anticipate, a cited reference must encompass each and every limitation of the putatively-anticipated claims. Here, the Sherr et al. reference is deficient in not teaching a p19ARF protein fragment, nor of teaching the use of either the p19ARF peptide or full-length p19 protein to inhibit proliferation of a tumor cell by contacting the tumor cell with either the full-length

protein or peptide. Accordingly, Applicants respectfully request that the Examiner withdraw rejection under 35 U.S.C. §102(b).

#### **IV. Claim Rejections Under 35 U.S.C. §103(a)**

The Action maintains the rejections of Claims 1 and 9-11 under 35 U.S.C. 103(a) as being unpatentable over Sherr et al. in view of Laes et al. (Cancer Genet Cytogenet 117:118-124, 2000) (hereinafter “Laes et al.”) The Action bases the rejection on its assertion that the phrase “p19ARF protein fragment that has the amino acid sequence as set forth in SEQ ID NO:10” is interpreted to include the full-length protein allegedly taught by Sherr et al.

As set forth in Part III above, the claim is directed to a method of inhibiting tumor cell growth comprising a step of inhibiting FoxM1B activity by contacting the cell with a p19ARF protein fragment that is less than the full-length protein. Sherr et al. merely relates to the full-length p19ARF. Sherr et al. did not demonstrate any p19ARF protein fragment, let alone the protein fragment having the sequence of SEQ ID NO: 10, that is capable of inhibiting tumor cell proliferation. Additionally, none of the most frequently mutated residues in the Ink4A/ p19ARF region in cancers falls within the sequence of SEQ ID NO: 10. For example, Gly-68, Pro-93, Arg-97, and Arg-114 are all outside amino acid residues 26-44. See Sherr et al. Col. 34, lines 56-62. It would not have been obvious to one skilled in the art the use of the p19ARF protein fragment having the sequence of SEQ ID NO: 10 for inhibiting proliferation of tumor cells based on Sherr *et al.*

The defect is not cured by Laes et al. Laes et al. does not teach or suggest which region of p19ARF is essential to its function. Laes et al. showed that in rodent hepatoma cells the p19ARF RNA is either absent or is expressed as a mutated form. In one mouse hepatoma cell line analyzed, the mutation would potentially encode a truncated p19ARF protein. The putative truncated p19ARF protein would retain only the N-terminal 15 amino acids of the wild type p19ARF. Laes et al. does not teach or suggest which portion of the large missing amino acid sequence (amino acid residues 16-169) is responsible for inhibiting tumor growth (Laes et al. Figure 2). Laes et al. does not teach or suggest the importance of amino acid residues 26-44 in inhibiting tumor growth. Moreover, Laes et al. does not teach or suggest whether a p19ARF

protein fragment, instead of the full length protein, can inhibit tumor cell proliferation. Thus, it would not have been obvious to one of skill in the art to use the p19ARF protein fragment having the sequence of SEQ ID NO:10 to treat a tumor cell with a reasonable expectation of success over Sherr et al. in view of Laes et al.

Additionally, neither Sherr et al, nor Laes et al., alone or in combination, teaches or suggests a method of inhibiting tumor cell growth comprising a step of inhibiting FoxM1B activity by the p19ARF peptide having the sequence of SEQ ID NO:10. It was the Applicants unexpected discovery that the p19ARF peptide inhibits FoxM1B activity. For example, Applicants unexpectedly discovered that p19ARF binds FoxM1B protein. See Example 15. Applicants also discovered that the p19ARF 26-44 sequence alone is sufficient to bind FoxM1B protein and inhibit FoxM1B transcriptional activity. See Example 18. Applicants further discovered that the p19ARF 26-44 peptide inhibits FoxM1B protein by sequestering FoxM1B in nucleolus. See Example 19. Additionally, Applicants disclosed that the p19ARF 26-44 peptide reduces FoxM1B-induced colony formation on soft agar. See Example 20. Neither Sherr et al., nor Laes et al., teaches or suggests the role of FoxM1B in tumor cell growth. Neither reference teaches or suggests the effect of a p19ARF protein fragment, much less the protein fragment as set forth in SEQ ID NO:10, on the transcriptional activity of FoxM1B.

Thus, claims 1, and 9-10 would not have been obvious to one skilled in the art in view of Sherr et al. and Laes et al., alone or in combination. Consequently, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

## **V. Conclusions**

Applicants respectfully contend that all conditions of patentability are met in the pending claims. Allowance of the claims is thereby respectfully solicited.

Once the claims are found allowable, Applicants respectfully request the Office reconsider and allow the non-elected species SEQ ID NOs:11 and 12, in the form of Examiner's Amendment. MPEP §809.02(a).

The Examiner in charge of this application is invited to contact the undersigned representative as indicated below if it is believed to be helpful.

Respectfully submitted,

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